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## EXTENDED REPORT

# Comparison of adding tocilizumab to methotrexate with switching to tocilizumab in patients with rheumatoid arthritis with inadequate response to methotrexate: 52-week results from a prospective, randomised, controlled study (SURPRISE study)

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## ABSTRACT

**Objective** To compare the efficacy and safety between tocilizumab added to methotrexate and tocilizumab switched from methotrexate in patients with active rheumatoid arthritis (RA).

**Methods** This is a 2-year randomised, controlled study. RA patients with moderate or high disease activity despite methotrexate were randomly assigned either to tocilizumab added to methotrexate (add-on) or tocilizumab switched from methotrexate (switch). The primary endpoint was the DAS28 remission rate at week 24. Secondary objectives included other clinical efficacy indices, radiological outcomes assessed with the van der Heijde-modified total Sharp scoring system (mTSS), and safety.

**Results** Of 223 randomised patients, 83% completed 52 weeks. DAS28 remission rates at week 24 were 70% for add-on and 55% for switch ( $p=0.02$ ), but they became comparable at week 52 (72% vs 70%,  $p=0.86$ ). Structural remission rates ( $mTSS \leq 0.5$ ) at week 52 were not different (66% vs 64%,  $p=0.92$ ). However, clinically relevant radiographic progression rates (CRRP;  $mTSS \geq 3$ ) tended to be higher with the switch than with the add-on (15% vs 7%,  $p=0.07$ ). Radiographic progression in the CRRP patients was larger with the switch than with the add-on (9.0/year vs 5.0/year,  $p=0.04$ ). The difference in the mean C-reactive protein of the CRRP patients was significant for the first 24 weeks (1.56 vs 0.49,  $p=0.001$ ) but not for the following 28 weeks (0.10 vs 0.04,  $p=0.1$ ). Overall safety was preferable in the switch group.

**Conclusions** In RA patients with inadequate response to methotrexate, tocilizumab added to methotrexate more rapidly suppressed inflammation than tocilizumab switched from methotrexate, leading to superior clinical efficacy and prevention of joint destruction.

**Trial registration number** NCT01120366.

## INTRODUCTION

The advent of intermittent methotrexate (MTX) and various biologic agents has had such an impact

on the treatment of rheumatoid arthritis (RA) that a paradigm shift has emerged towards earlier and more aggressive intervention with the goal of remission.<sup>1–3</sup> MTX is an anchor drug in the management of RA because of its long-term effectiveness and safety profile,<sup>4</sup> but in patients who have responded insufficiently to MTX, adjustment of treatment should be considered, including the introduction of another conventional disease-modifying anti-rheumatic drug (DMARD) or a biological DMARD according to the absence/presence of poor prognostic factors.<sup>1</sup>

When starting a biological DMARD in MTX-insufficient responders with poor prognostic factors, there are two strategies: one is combining a biological DMARD with MTX, and the other is switching to a biological DMARD from MTX. While majority of clinical studies provide the favourability of a combination therapy, the switch to a monotherapy is debate for interleukin-6 (IL-6) blocking.

Regarding tumour necrosis factor (TNF) inhibitors, results from many clinical studies have suggested that the use of TNF inhibitors in combination with MTX is superior to TNF inhibitor monotherapy, and that adding TNF inhibitors to MTX is better than replacing MTX with TNF inhibitors in efficacy, while the safety is comparable among the groups.<sup>5–7</sup>

Tocilizumab (TCZ), humanised antihuman IL-6 receptor monoclonal antibody, has been proven to be efficacious in RA patients, and its efficacy has been well validated, both as a combination therapy with MTX and as monotherapy. TCZ monotherapy has been shown to be more efficacious than MTX monotherapy in MTX-naïve patients, in patients with an inadequate response to MTX and in patients with a history of MTX treatment more than 6 months before.<sup>8–10</sup> Therefore, a question arises if addition of TCZ to MTX or a switch from MTX to TCZ is comparable.

The ACT-RAY study was designed as a 3-year trial to compare adding TCZ to switching to TCZ



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in inadequate responders to MTX. In that study, no clinically relevant superiority of the addition of TCZ to MTX over the switch to TCZ monotherapy was proven, but there was a modest difference favouring the addition strategy in achieving low disease activity at week 24 and in suppressing radiographic progression at week 52.<sup>11 12</sup>

The present 2-year study, the Success of Tocilizumab in RA Patients With Remission Induction and Sustained Efficacy After Discontinuation (SURPRISE) study, was planned to evaluate the efficacy and safety profile of adding TCZ to MTX or switching MTX to TCZ in patients with moderate or high disease activity despite MTX treatment during the first 52 weeks and subsequently to determine if maintenance of remission after discontinuation of TCZ is possible between weeks 52 and 104. The first-year results are reported here.

## SUBJECTS AND METHODS

### Study design and participants

In this randomised, controlled study, patients with RA diagnosed according to the 1987 American College of Rheumatology (ACR) criteria less than 10 years before, aged between 20 and 75 years, with moderate or high disease activity at baseline visits, were enrolled between November 2009 and March 2012. Moderate or high disease activity was defined as a disease activity score in 28 joints (DAS28; on the basis of the erythrocyte sedimentation rate, ESR) of more than 3.2. Participants had to have been receiving stable doses of  $\geq 6$  mg/week of MTX for treatment of RA for at least 8 weeks before enrolment.<sup>9</sup> Patients were excluded if they had previously taken or were taking any biologic treatment, leflunomide within 12 weeks of baseline, tacrolimus within 4 weeks, or any other conventional DMARDs other than MTX within 8 weeks. Patients taking prednisolone (or equivalent) at a dose of more than 10 mg/day were excluded.

This report covers the planned analysis of the first 1 year of a 2-year study (NCT01120366, UMIN000002744). This study was approved by the ethics committee at each site and conducted in accordance with the Declaration of Helsinki. All participants gave their written, informed consent.

### Study treatment

Patients were randomly assigned by a centralised system in a 1:1 ratio to one of two open-label treatment groups: TCZ added to MTX (ADD-ON group) or TCZ switched from MTX

(SWITCH group). TCZ was administered at a dose of 8 mg/kg intravenously every 4 weeks, and MTX was maintained at the same dose as the baseline unless a clinically relevant adverse event (AE) occurred.

### Collected patient data and assessments

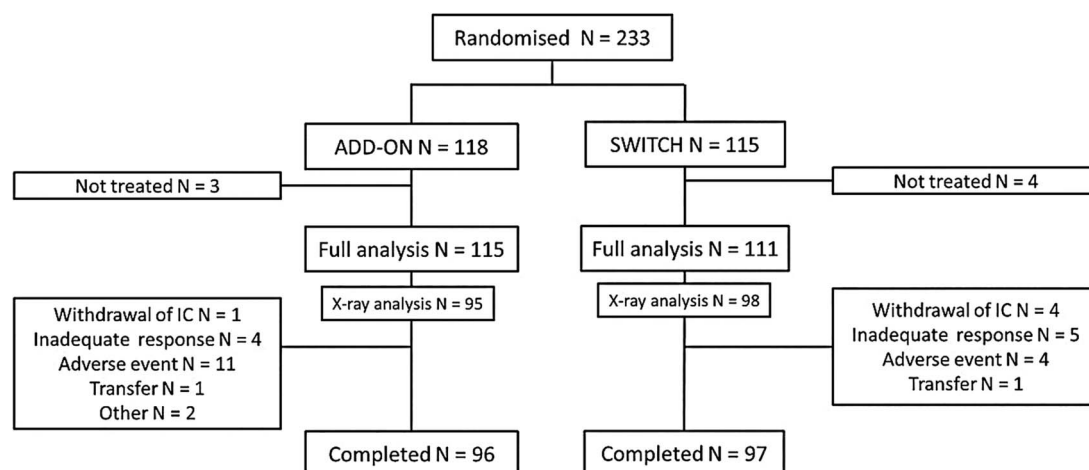
Data collected at baseline included demographics and disease characteristics. The following parameters were assessed at baseline and at weeks 4, 12, 24, and 52: tender joint count, swollen joint count, health assessment questionnaire-disability index, patient global assessment using a visual analogue scale (VAS), evaluator global assessment using a VAS, C-reactive protein (CRP), ESR and matrix metalloproteinase-3. Radiographs of the hands and feet were obtained at baseline and at week 52. Each radiograph was assessed applying the van der Heijde-modified total Sharp scoring system (mTSS) by two independent readers who were blinded to treatment assignment and the patient's clinical status. At each visit, patients were monitored for physical signs, laboratory tests, and AEs.

### Statistical analysis

The primary outcome of this study was defined as the percentage of patients in remission according to the DAS28-ESR at week 24. With the assumption that DAS28-ESR remission would be achieved by 50% of patients in the ADD-ON group and 45% in the SWITCH group, 133 patients per treatment group were calculated as necessary for more than 80% power to prove the null hypothesis of no difference between the treatment arms with a non-inferiority margin of 10%. A two-sided statistical test of no difference at the 5% significance level was used. As a sensitivity analysis, the percentage of patients in remission according to the simplified disease activity index (SDAI) and clinical disease activity index (CDAI) in substitution for the DAS28 was further analysed.

Efficacy analyses were conducted in the full analysis population with the last-observation-carried-forward method. Safety endpoints including the incidence of AEs, serious AEs, infections, and specific laboratory abnormalities were analysed in all treated patients.

All analyses of proportions were analysed for treatment differences with the  $\chi^2$  test, and continuous variables were compared with Student's *t* test.



**Figure 1** Patient disposition and study flow chart. IC, informed consent.

## RESULTS

## Patient flow and baseline characteristics

Figure 1 shows patient disposition through the 52 weeks. A total of 223 patients eligible for this study were randomised to TCZ added to MTX (ADD-ON, N=118) or TCZ switched from MTX (SWITCH, N=115). Of all of the patients randomly assigned, three patients in the ADD-ON group and four in the SWITCH group were not treated with TCZ and excluded from the analysis. Overall, 115 in the ADD-ON group and 111 in the SWITCH group who received at least one injection of TCZ were analysed for efficacy and safety as the full analysis population. The number of patients in the analysis did not reach the sample size defined in the protocol to prove the inferiority of switch strategy to add-on. There were no statistically or clinically significant differences between the two groups in baseline characteristics, except for the swollen joint count in the 66 joints (table 1).

Twenty patients in the ADD-ON group and 13 in the SWITCH group lacked X-rays of the hands and feet at baseline or week 52 and were excluded from the radiographic analysis. The baseline characteristics did not differ significantly between the patients who underwent radiographic evaluation and those who did not (data not shown).

## Clinical efficacy

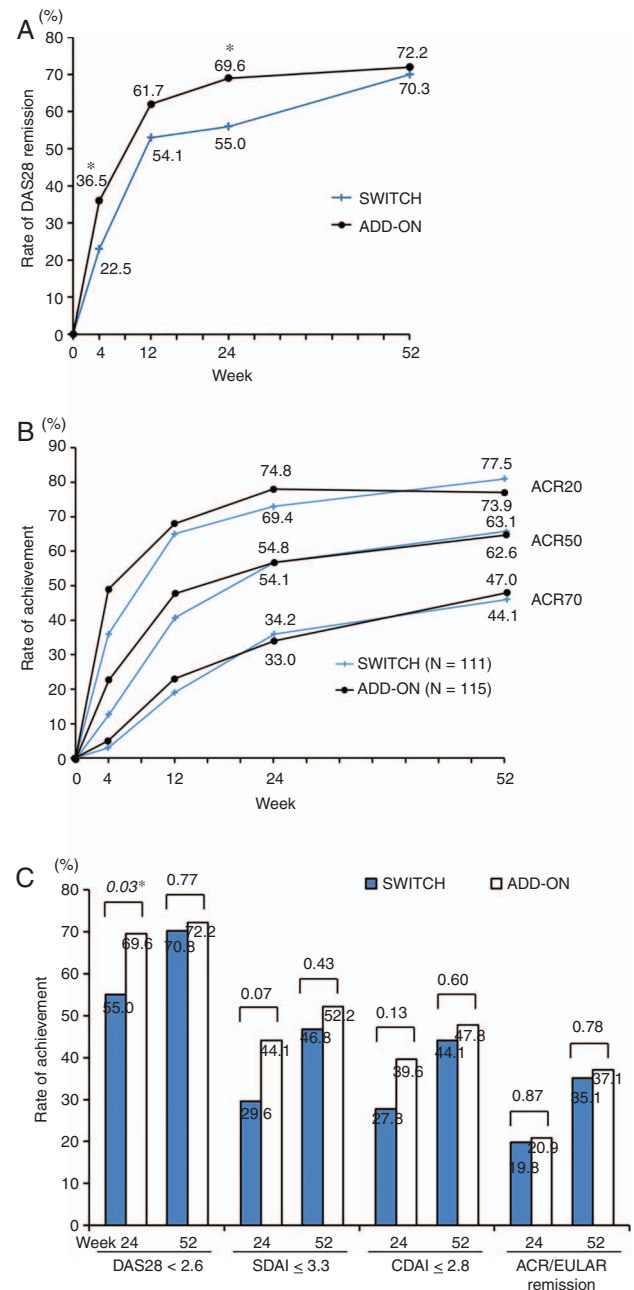
The main efficacy results at weeks 24 and 52 are summarised in figure 2 and online supplementary table. DAS28-ESR remission rates were significantly higher in the ADD-ON group than in the SWITCH group at weeks 4 and 24 (primary endpoint), but they became comparable at week 52 (figure 2A). Remission rates

**Table 1** Baseline patient characteristics

	ADD-ON (N=115)	SWITCH (N=111)	p Value
Age, years	55.8 (11.7)	56.3 (2.7)	0.60
Female, N (%)	100 (87.0)	96 (86.5)	1.00
Weight, kg	55.5 (10.8)	54.2 (9.6)	0.41
Disease duration, years	3.6 (3.2)	3.8 (3.1)	0.38
Methotrexate dose, mg/week	8.6 (2.5)	8.4 (2.0)	0.88
Methotrexate duration, months	21.1 (28.5)	20.6 (24.6)	0.88
Prednisolone use, N (%)	41 (35.7)	41 (36.9)	0.84
Prednisolone dose, mg/day	4.3 (2.1)	5.0 (2.8)	0.31
TJC28	7.1 (5.3)	7.2 (6.0)	0.65
SJC28	6.3 (4.2)	7.2 (4.9)	0.23
TJC68	9.6 (7.5)	10.1 (9.0)	0.93
SJC66	7.6 (5.3)	9.9 (7.6)	0.02*
CRP, mg/dL	1.2 (1.5)	1.8 (2.6)	0.58
ESR, mm/h	40.8 (28.0)	44.7 (29.6)	0.27
PGA, mm	46 (23)	51 (24)	0.15
EGA, mm	46 (21)	47 (21)	0.47
DAS28-ESR	5.1 (1.1)	5.3 (1.2)	0.29
SDAI	23.9 (10.9)	26.1 (13.4)	0.32
CDAI	22.6 (10.4)	24.2 (12.2)	0.40
HAQ-DI	1.0 (0.7)	1.0 (0.7)	0.42
MMP-3, mg/dL	172.1 (152.4)	190.4 (199.1)	0.96

\*p<0.05.

CDAI, clinical disease activity index; CRP, C-reactive protein; DAS28, disease activity score for 28 joints; EGA, evaluator global assessment; ESR, erythrocyte sedimentation rate; HAQ-DI, health assessment questionnaire disability index; MMP, matrix metalloproteinase; PGA, patient global assessment; SDAI, simplified disease activity index; SJC, swollen joint count; TJC, tender joint count.



**Figure 2** Clinical efficacy results. Results over time for (A) percentage of patients achieving DAS28 remission, (B) percentage of patients achieving ACR20/50/70, (C) patients achieving remission according to DAS28, SDAI, CDAI and ACR/EULAR Boolean defined criteria at weeks 24 and 52. DAS28, disease activity score for 28 joints; ACR, American College of Rheumatology; SDAI, simplified disease activity index; CDAI, clinical disease activity index; EULAR, European League against Rheumatism. \*p<0.05.

according to the SDAI and the CDAI were not significantly different between the two groups but showed a similar tendency (see online supplementary figure A, B). For other endpoints, including Boolean remission and ACR20/50/70, the differences between the two treatment groups were not significant, but there was a trend towards superiority of TCZ added to MTX to TCZ switched from MTX (figure 2B, C, see online supplementary table). Although the week 8 visit was not compulsory, data were collected for 55% of the patients and analysed. The DAS28-ESR remission rate was also significantly higher in the ADD-ON group at week 8 (see online supplementary figure C), and this

corroborated the finding that TCZ added to MTX was favourable for the 24 weeks. The clinical efficacy of TCZ switched from MTX could catch up by week 52.

### Structural outcome

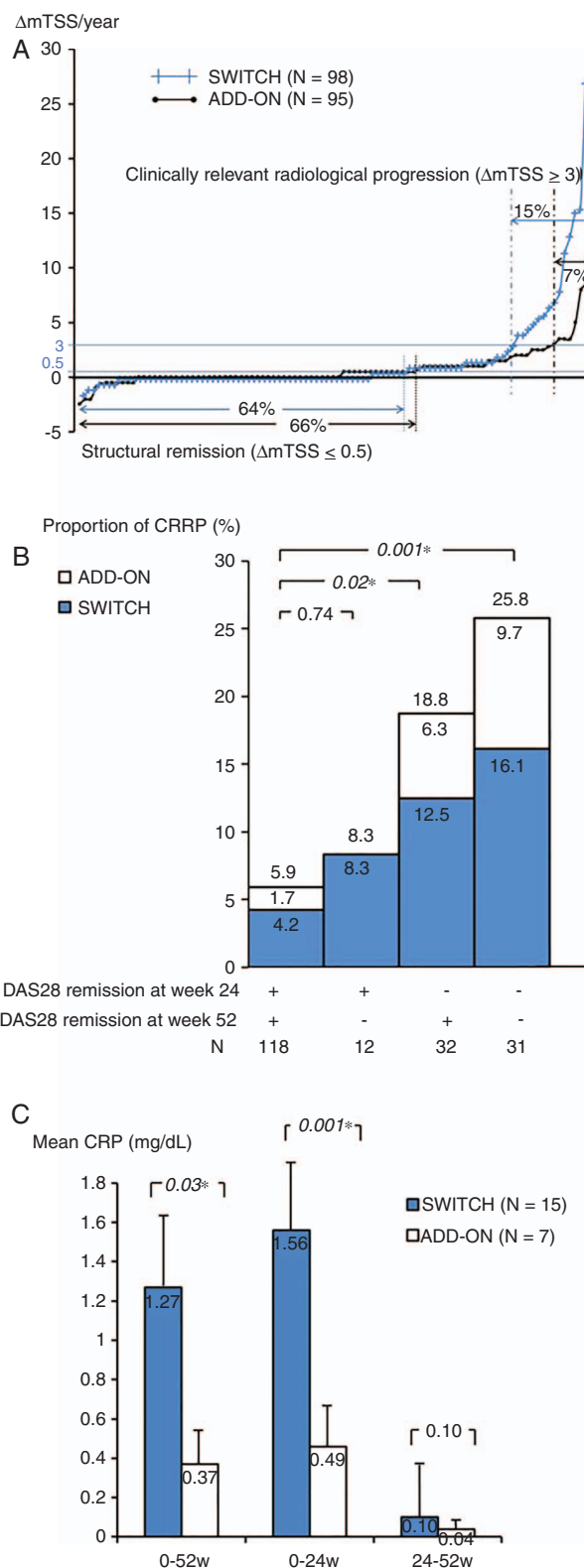
At week 52, structural remission, defined as a change in mTSS from baseline  $\leq 0.5$ , was achieved in 63 patients (66%) in the ADD-ON group and in 63 (64%) in the SWITCH group ( $p=0.92$ ), and there was no significant difference in the median change (0 in both groups) between the two groups. Clinically relevant radiographic progression (CRRP), defined as change in mTSS from baseline  $\geq 3$ , was observed in 7 patients (7%) in the ADD-ON group and 15 (15%) in the SWITCH group. Although the percentages of CRRP were not significantly different between the two groups ( $p=0.07$ ), the mean change in mTSS in CRRP patients was significantly larger in the SWITCH group than in the ADD-ON group (9.0/year vs 5.0/year,  $p=0.04$ , figure 3A).

To examine the relationship between the achievement of DAS28-ESR remission at week 24 and the CRRP (figure 3B), the patients were divided into four groups: remission at both weeks 24 and 52 (68 in the ADD-ON group and 50 in the SWITCH group); remission at week 24 but non-remission at week 52 (6 in both groups); non-remission at week 24 but remission at week 52 (9 in the ADD-ON group and 23 in the SWITCH group); and non-remission at weeks 24 and 52 (12 in the ADD-ON group and 19 in the SWITCH group). The proportion of CRRP patients was the lowest in the group with remission at both weeks 24 and 52, and significantly less than the group with non-remission at week 24 but remission at week 52 and the group with non-remission at weeks 24 and 52 (5.9% vs 18.8%,  $p=0.02$ ; 5.9% vs 25.8%,  $p=0.001$ , respectively). The group with remission at week 24 but non-remission at week 52 showed a comparable percentage of CRRP patients as the group with remission at both weeks 24 and 52, implying that non-remission at week 24 contributed chiefly to rapid radiological progression. In addition, the CRRP patients included nearly twice as many SWITCH patients as ADD-ON patients, supporting the idea that the add-on strategy is a good strategy for preventing radiological progression.

Inflammation status using CRP was further analysed through the study of the CRRP patients, who had higher disease activity than those who responded well to TCZ (figure 3C). The mean CRP of the CRRP patients for 52 weeks was much higher in the SWITCH group than in the ADD-ON group (1.27 vs 0.37,  $p=0.03$ ). The difference in the mean CRP between the two groups was significant for the first 24 weeks (1.56 vs 0.49,  $p=0.001$ ) but not for the second 28 weeks (0.10 vs 0.04,  $p=0.1$ ), suggesting that less radiographic progression in TCZ added to MTX was attributable to the degree inflammation was suppressed during the first 24 weeks of the study.

### Safety

The safety results are presented in table 2. Overall, the number of patients with at least one AE was greater in the ADD-ON group than in the SWITCH group (60.0% vs 45.0%,  $p=0.02$ ), but the percentage of patients with at least one serious AE was comparable in the two treatment groups (13.9% vs 8.1%,  $p=0.20$ ). AEs occurring more in the ADD-ON group than in the SWITCH group were infections, gastrointestinal disorders, and liver dysfunction. Eleven patients (9.6%) in the ADD-ON group and 4 (3.6%) in the SWITCH group were withdrawn



**Figure 3** Structural outcome. (A) Cumulative probability plot of change from baseline to week 52 in van der Heijde-modified total Sharp scoring system (mTSS). (B) Percentage of patients with CRRP. (C) Mean CRP. CRRP, clinically relevant radiographic progression; DAS28, disease activity score for 28 joints; CRP, C-reactive protein. \* $p<0.05$ .

from the study because of AEs ( $p=0.11$ ). There was one death from interstitial pneumonitis in the ADD-ON group in this 1-year observation period.



**Table 2** Adverse events by group

	ADD-ON (N=115)		SWITCH (N=111)	
	AE 69, 60.0%	SAE 16, 13.9%	AE 50, 45.0%	SAE 9, 8.1%
<b>Total patients with <math>\geq 1</math> AE or <math>\geq 1</math> SAE</b>				
Infections and infestations	47, 40.9%	6, 5.2%	25, 22.5%	7, 6.3%
Bacterial pneumonia	2, 1.7%	2, 1.7%	3, 2.7%	1, 0.9%
Nasopharyngitis	10, 8.7%	0	3, 2.7%	1, 0.9%
Gastrointestinal disorders	29, 25.2%	1, 0.9%	14, 12.6%	2, 1.8%
Hepatobiliary disorders	22, 19.1%	1, 0.9%	5, 4.5%	1, 0.9%
Liver function disorders	15, 13.0%	1, 0.9%	3, 2.7%	0
Respiratory, thoracic and mediastinal disorders	14, 12.2%	1, 0.9%	5, 4.5%	0
Laboratory test abnormalities	18, 15.7%	0	9, 8.1%	0
Metabolism and nutrition disorders	9, 7.8%	0	7, 6.3%	0
Skin and subcutaneous tissue disorders	7, 6.1%	0	7, 6.3%	2, 1.8%
Injury, poisoning, and procedural complications	7, 6.1%	4, 3.5%	2, 1.8%	1, 0.9%
General disorders and administration site conditions	4, 3.5%	0	1, 0.9%	0
Neoplasms benign, malignant, unspecified	2, 1.7%	2, 1.7%	1, 0.9%	0
Eye disorders	3, 2.6%	0	0	0
Musculoskeletal and connective tissue disorders	2, 1.7%	1, 0.9%	1, 0.9%	0
Blood and lymphatic system disorders	2, 1.7%	1, 0.9%	1, 0.9%	0

AE, adverse event; SAE, serious adverse event.

## DISCUSSION

This study compared two different strategies in patients with RA with inadequate responses to MTX, and the results suggest that TCZ added to MTX is clinically and radiographically superior to TCZ switched from MTX. The switch strategy was able to catch up later to the add-on protocol with respect to clinical efficacy, but the structural damage progressed more in a year with the switch therapy.

TCZ monotherapy as well as TCZ in combination with MTX has been proven to be more efficacious than MTX monotherapy.<sup>8–10 13 14</sup> The ACT-RAY study comparing the efficacy and safety of TCZ in combination with MTX with TCZ monotherapy in a similar fashion to the present study showed no clinically relevant superiority of the add-on strategy over the switch strategy at 1 year and suggested that TCZ monotherapy is a valuable treatment in RA patients with inadequate response to MTX.<sup>11 12</sup> However, a modest difference favouring the add-on strategy in achieving low disease activity at week 24 and in suppressing radiographic progression at week 52 was observed. The present study underlined the trends showing the clinical superiority of the combination therapy for the first half of the follow-up period and radiological superiority at 1 year. The mean disease duration in the SURPRISE study (3.6–3.8 years) was shorter than that in the ACT-RAY study (8.2–8.3 years). In the ACT-RAY study, conventional DMARDs were added in a patient with a DAS28 >3.2 at week 24. Those differences in patient background and study protocol between the two studies could generate more notable advantageous results of add-on strategy in our study. The CHARISMA study, in which the combination therapy of TCZ was compared with TCZ monotherapy as a part of a dose-finding phase 2 trial in RA patients who had an incomplete response to MTX, also implied that combination therapy was superior to monotherapy;<sup>15</sup> DAS28 remission rates at week 16 in that study were 34% for combination therapy and 17% for monotherapy. We assume that stopping MTX in conjunction with starting TCZ could transiently increase disease activity, since MTX might have worked to

downregulate inflammation to some extent despite the inadequacy.

Importantly, the worse disease activity in patients with TCZ switched from MTX in the first 24 weeks impacted radiological outcomes at week 52, despite comparable clinical efficacy at week 52. This finding was observed in another trial conducted in Japan in which patients completing a 26-week, randomised, placebo-controlled trial of adalimumab received open-label adalimumab in the following 26 weeks. This study showed that the accrual of significant structural damage during 26-week placebo therapy contributed to the persistence of differences in radiographic progression at week 52.<sup>16</sup> Taking those findings together with the irreversible nature of the structural damage, TCZ added to MTX was better than TCZ switched from MTX.

Despite the clinical and radiological superiority of TCZ added to MTX, TCZ switched from MTX showed favourable safety outcomes. While serious AEs were comparable between the two study treatments, AE rates were higher with the add-on strategy than with the switch strategy. In particular, the add-on strategy resulted in a higher proportion of patients with hepatic disorder. This was also observed in other TCZ studies,<sup>11–13 17</sup> suggesting that the combination of TCZ and MTX might have a synergistic effect on the liver. Nevertheless, the regimen in the combination group in the present study was well tolerated.

The fact that the clinical efficacy of SWITCH eventually caught up to that of ADD-ON would be provoking a new strategy: stopping or decreasing MTX after TCZ has made a sufficient contribution. Aside from the fact that stopping MTX is sometimes necessary because of liver injury or gastrointestinal discomfort, the lymphoproliferative disorder related to long-term use of MTX increasingly poses a serious problem leading us to surmise that minimising the use of MTX is preferable.<sup>18–20</sup> This should be further examined in future studies.

The present study has several limitations. First, this study was not double-blind, and it cannot be ruled out that knowing the treatment might affect the clinical evaluation. However, since an objective index such as the mTSS that was assessed by

independent blinded readers could detect a difference between the two groups, this effect was likely minimal. Second, the number of patients enrolled in this study did not reach the sample size defined in advance to prove non-inferiority of TCZ switched from MTX to TCZ added to MTX. Although the add-on strategy was significantly superior to the switch strategy on the primary endpoint using the DAS28, the superiority in the sensitivity analysis using the SDAI and the CDAI was limited because of the insufficient power. Third, the dose of MTX used in this study was lower than that used in Western countries, as in the ACT-RAY study. Since the lower dose of MTX would have tended to decrease the difference between the two groups, this did not appear to have affected the results of the study. In addition, it has been reported<sup>21</sup> that concentration of MTX polyglutamates, a potential marker for MTX use, in red blood cells was relatively higher in a Japanese study than in a study from the USA, suggesting that a lower dose of MTX may be sufficient in Japanese patients.

In conclusion, in RA patients with inadequate response to MTX, TCZ added to MTX suppresses inflammation more than TCZ switched from MTX, leading to superior clinical efficacy and prevention of joint destruction. While meaningful clinical and radiographic responses were achieved with both strategies, patients could benefit from combination therapy more than monotherapy, although precautions against AEs are necessary.

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**Supplementary table**

	Week 24			Week 52		
	ADD-ON (N = 115)	SWITCH (N = 111)	p value	ADD-ON (N = 115)	SWITCH (N = 111)	p value
DAS28 remission rate (%)	69.6	55.0	0.03*	72.2	70.3	0.77
Change in DAS28	-2.9 (1.3)	-2.7 (1.5)	0.41	-3.0 (1.4)	-3.0 (1.6)	0.79
EULAR good/moderate responders (%)	96.5	90.1	0.06	94.8	88.3	0.10
Boolean remission rate (%)	20.9	19.8	0.87	37.1	35.1	0.78
SDAI remission rate (%)	44.1	29.6	0.07	52.2	46.8	0.43
CDAI remission rate (%)	39.6	27.8	0.13	47.8	44.1	0.60
Change in PGA (mm)	-23 (26)	-25 (28)	0.99	-2.6 (29)	-3.0 (28)	0.38
Change in EGA (mm)	-34 (22)	-31 (23)	0.48	-3.5 (23)	-3.4 (22)	0.97
Change in pain VAS (mm)	-26 (26)	-25 (28)	0.36	-2.8 (30)	-3.0 (28)	0.75
Change in HAQ-DI	-0.4 (0.5)	-0.4 (0.6)	0.75	-0.4 (0.6)	-0.5 (0.6)	0.50
Change in ESR (mm/h)	-31.6 (25.1)	-34.5 (29.7)	0.69	-31.0 (25.4)	-34.0 (29.9)	0.70
Change in CRP (mg/dL)	-0.8 (3.8)	-1.7 (2.6)	0.49	-0.7 (3.8)	-1.7 (2.6)	0.25



Change in SJC28	-5.1 (3.8)	-5.4 (5.0)	0.66	-5.2 (4.0)	-5.7 (4.9)	0.32
Change in TJC28	-5.2 (5.0)	-4.9 (5.3)	0.65	-5.2 (5.3)	-5.3(5.6)	1.00

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DAS28, disease activity score for 28 joints; EULAR, European League Against Rheumatism; SDAI, simplified disease activity index, CDAI, clinical disease activity index; PGA, patient global assessment, EGA, evaluator global assessment; EGA, evaluator general assessment; VAS, visual analogue scale; HAQ-DI, health assessment questionnaire disability index; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; SJC, swollen joint count; TJC, tender joint count

\*,  $p < 0.05$

**Supplementary figure.** (A) Percentage of patients achieving SDAI remission. (B) Percentage of patients achieving CDAI remission. (C) Results over time for percentage of patients achieving DAS28 remission with results at week 8. DAS28, disease activity score for 28 joints; SDAI, simplified disease activity index; CDAI, clinical disease activity index; .

